Text: Louise Hagbard, Ph.D. **Photo:** Ola Jacobsen

STEM CELL INNOVATORS

ABDENOUR SOUFI

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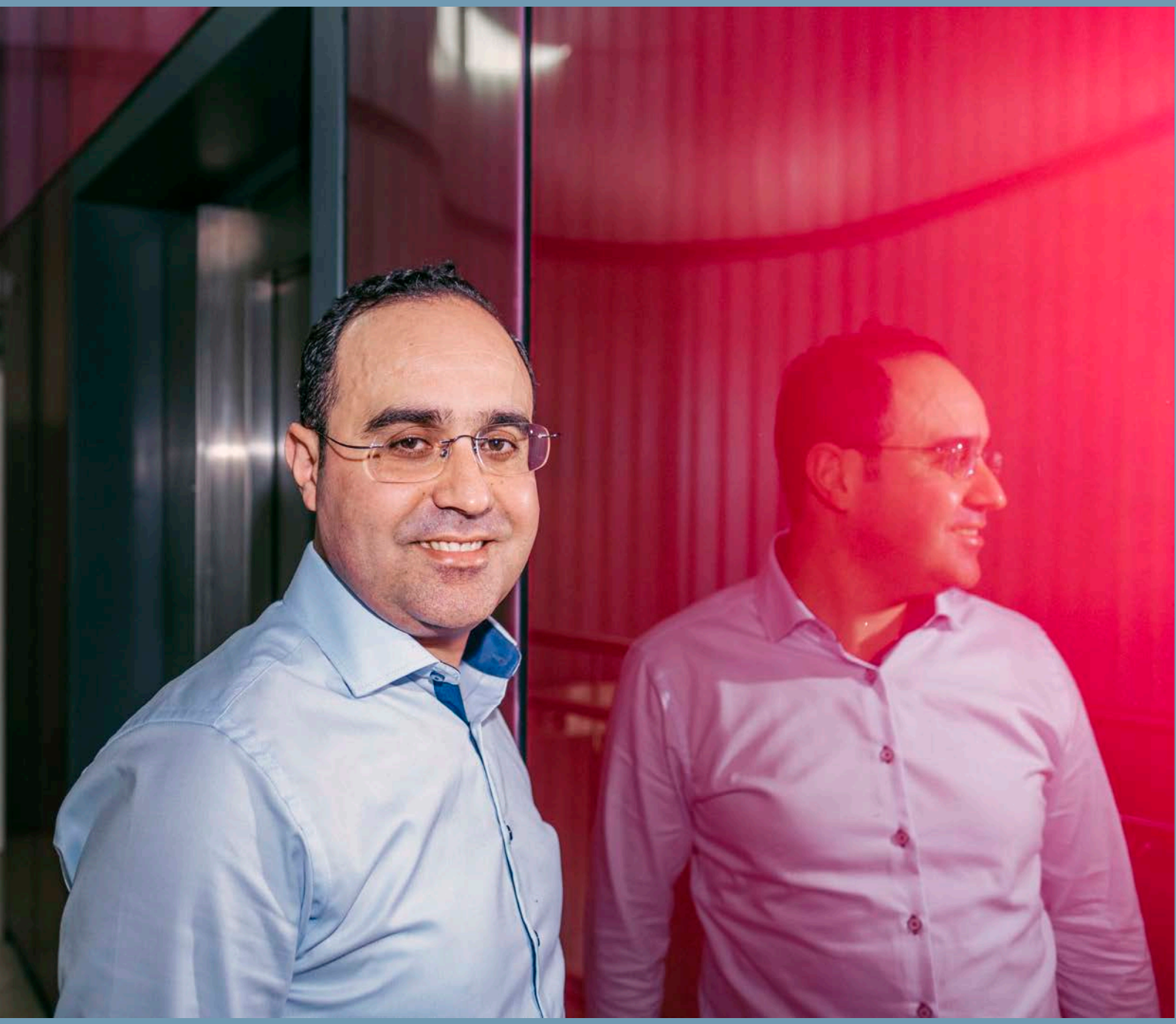
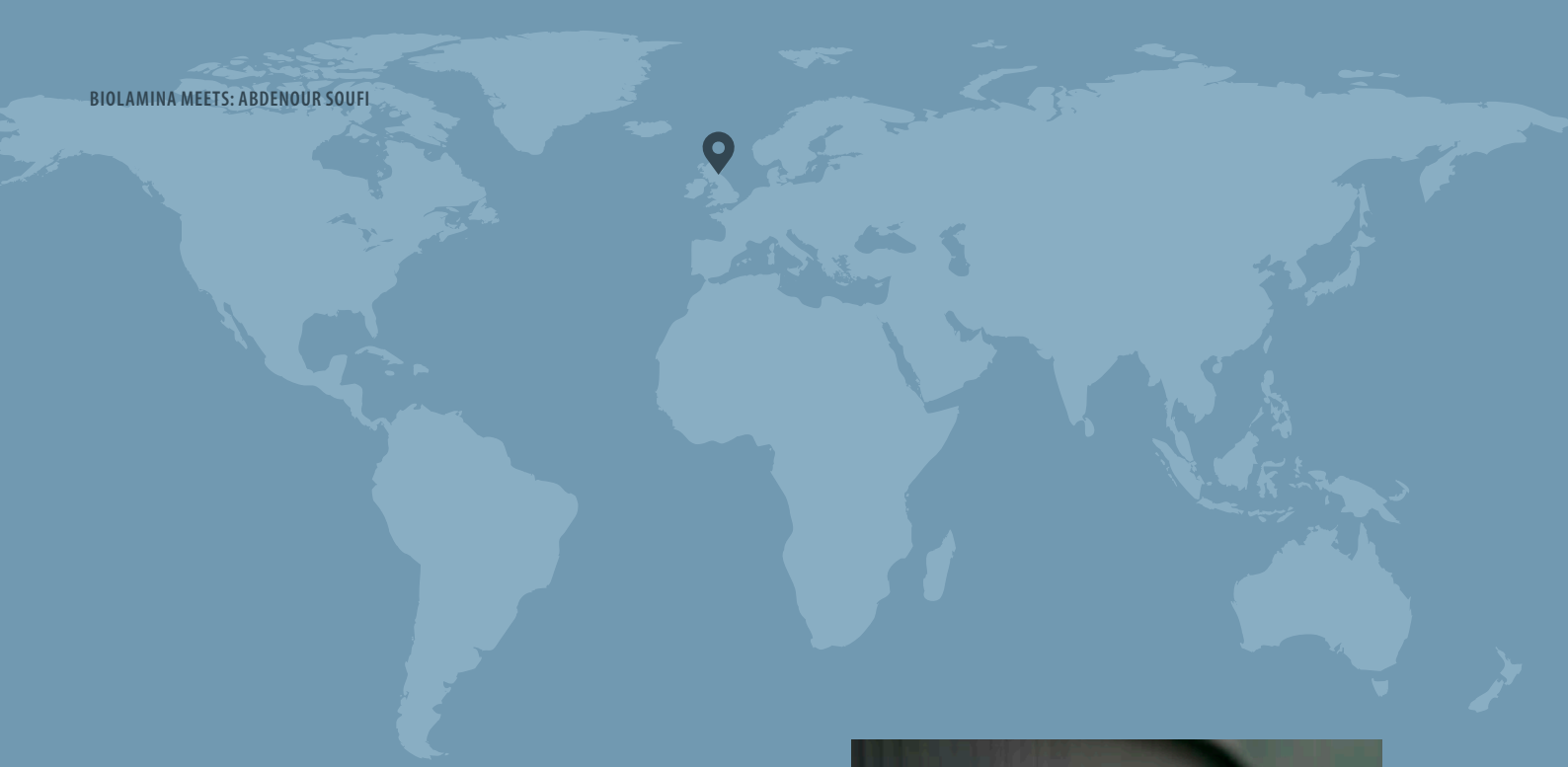
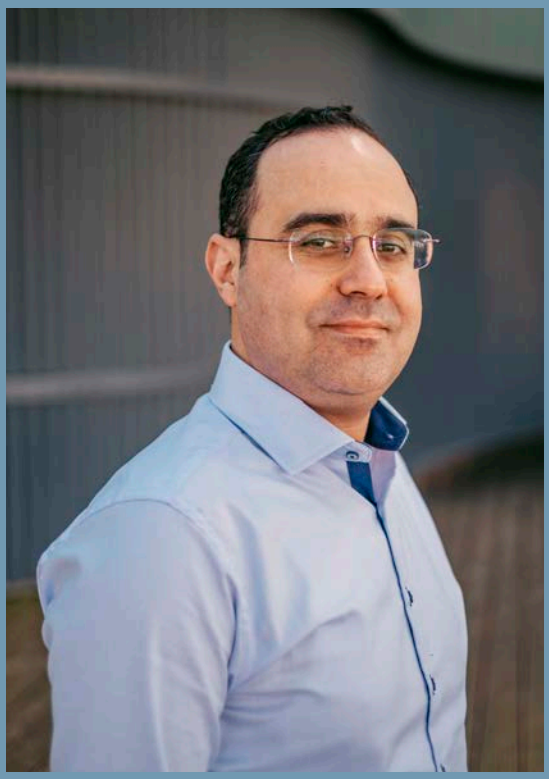




ABDENOUR SOUFI, PH.D.

SENIOR RESEARCHER AND GROUP LEADER, MRC CENTRE FOR REGENERATIVE MEDICINE, UNIVERSITY OF EDINBURGH, UK

ABOUT: **Dr. Abdenour Soufi is a group leader at the MRC Centre for Regenerative Medicine, University of Edinburgh, UK. His research group focuses on the engineering of highly potent, novel iPSC reprogramming factors.**



MRC CENTRE FOR REGENERATIVE MEDICINE

The MRC Centre for Regenerative Medicine (CRM) is a part of the University of Edinburgh, located at the Edinburgh BioQuarter site. The Centre is led by the Centre Director, Prof. Stuart Forbes and is a world leading, state-of-the-art facility, and a working place for almost 300 scientists and clinicians studying stem cells, disease and tissue repair. Research at the CRM is aimed at developing an understanding of the mechanisms underlying stem cell self-renewal and differentiation processes, and at developing new treatments for major diseases including cancer, heart disease, liver failure, diabetes, and Parkinson's.

"I always wanted to do science in Edinburgh, the birth place of Dolly, the land of the young (Nanog), and the landscape of Waddington."

How did you end up within the stem cell research field?

"I was born and raised in Algeria and during my studies there, I got a scholarship to study abroad. That was in 1997, and two things were happening that year that got me excited about science: that was the year Dolly was created, and the nucleosome structure was solved. Basically, the combination of these two is what I had been, and I am still working on. When I got my scholarship I moved to Bristol, where I did also my Ph.D. on a transcription factor interacting with chromatin, and I realized that this is what I want to work on. Working on stem cells followed later during my postdoctoral training at the University of Pennsylvania. During those years I focused on iPSC and reprogramming, working on the four Yamanaka Transcription factors and how they change the chromatin landscape of the genome by directly interacting with nucleosomes during reprogramming."

And how did you end up here, at the MRC Centre for Regenerative Medicine in Edinburgh?

"Looking back, it seems that I planned it all along. I remember when I first met Ian Chambers in 2010 and he asked me, 'What are you going to do next?' I replied, 'I am just finishing my postdoc and I'll come and join you in Edinburgh.' I always wanted to do science in Edinburgh, the birth place of Dolly, the land of the young (Nanog), and the landscape of Waddington. These symbolize reprogramming, stem cells and epigenetics, which what I am interested in. So Edinburgh is perfect for me. Even though this is what ended up happening, the reality was that I applied for a Chancellor's fellowship after finishing my postdoc and started my lab here at the MRC CRM in 2015."

What is your aspiration for your research field? Where are you going with your research?

"Obviously, we are mainly an iPS cell lab and our focus is specifically to define how chromatin is shaped inside the nucleus and how we can control cell identity in general. We aspire to find a way to tickle the genome at the right places so the cell will respond in a controlled way, and be persuaded to change its identity. Really, what I would like to see in my lifetime is a point where we can control cell identity *in vivo*. I mean a very precise, molecular interaction way of control, rather than just throwing things at cells. Being able to control cell identity at will, to regenerate organs and tissues, that would be my aspiration."

Do you work with human embryonic stem cells? What is your opinion about the difference between them?

"Yeah, we work with both ES and iPS cells. I think from our perspective there is no difference between ES and iPS. If you compare many established ES lines, they show similar variability in terms of the differentiation capacity as seen in iPS lines, so no difference there. However, we know iPS reprogramming itself can create additional genetic and epigenetics modifications that might not necessarily be obvious if you are not looking for them, and those might not be the same in ES, I think. Overexpression of transcription factors and other handling techniques obviously does a lot to the cell and the genome. So, we believe that these unwanted genetic and epigenetic changes are acquired during the reprogramming process. That's why we're interested in this, to make it better."

"In terms of ES cells, they have their own problems. For example, getting the cells to start with is ethically restricted and not really practical. It's easier for example, to generate a large number of iPS-lines from different patients to model different diseases. Doing the same using ES lines is not really possible, even though there are some lines for specific diseases available.

"So, from a research point of view, we welcome iPS cells, and we want to push them further, make it more applicable, more economical, and definitely safer. It's hard for me to imagine that the problems with ES cells will be solved in the future, so I don't think using ES cells will expand beyond its current state. On the contrary, working with iPS cells is growing and becoming simpler, and I think whatever problems are currently facing iPS cells will, hopefully, be solved in the near future."

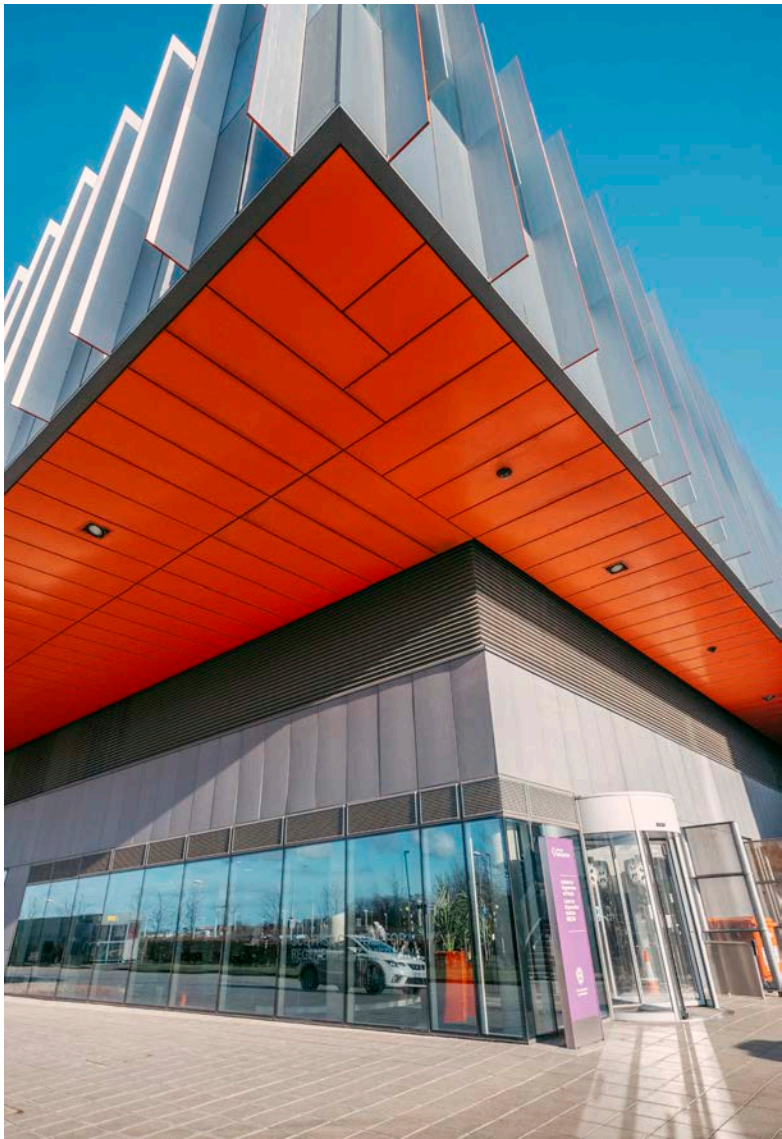
Then you have the million-dollar question. What is a pluripotent stem cell?

"Yeah. I wish I could answer you. There is no set standard for pluripotency. To call human stem cells pluripotent, you basically have to somehow prove that they can make cells from the three germ layer. This is usually done using teratoma assays or *in vitro* differentiation. The other way is to show how similar these cells are to well-established ES lines by comparing gene expression profiles or other known pluripotency markers. With the mouse system, pluripotency of stem cells can be functionally measured *in vivo* by how much they contribute to chimeras or ultimately generating the whole animal. That's the holy grail of pluripotency. For human, that's not possible obviously. Because many things can cause teratomas, I don't think it is a good measurement of pluripotency. Also, using RNA-seq to compare gene expression will depend on what you are comparing it to. So, I think for the human field it's harder to establish what pluripotency means. The potential of stem cells to make the three germ layers is basically what pluripotency means at the moment."

What do you think about the CRISPR techniques?

"I think it is going to be a big part of the future, but at the same time we should not rush the technology. We have to be careful not to sell hype to people because, as simple and as standard as people might think, in reality, when you go to a lab it's not as simple and it doesn't always work.

↓ With new state-of-the-art facilities and a 270+ team of scientists and clinicians, CRM is positioned uniquely to translate scientific knowledge to industry and the clinic. Research at CRM is aimed at gaining fundamental understanding of stem cells at to use this knowledge to develop new treatments for major diseases including cancer, heart disease, liver failure, diabetes, multiple sclerosis and Parkinson's.



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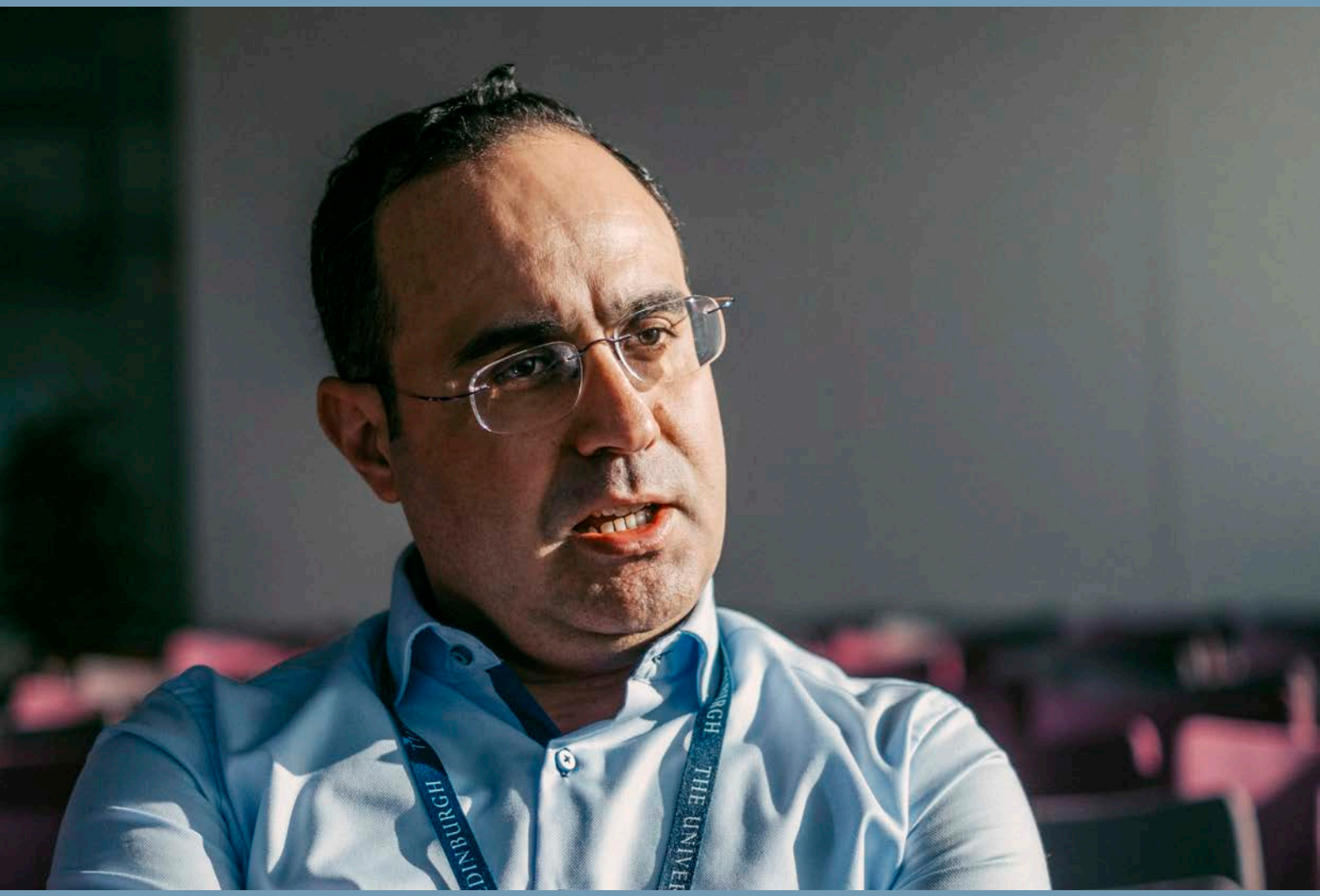

"To culture hES cells used to be an art and not a science. Now anybody can do it and reproduce the data."

If you would evaluate the protocols that you're using today, do you feel that they are robust or reproducible?

"I think yes, although it took us a while. For example, culturing human ES cells to maintain a pluripotent state used to be an art form not science. Now thanks to defined media and the Biolaminin 521 substrate it became a standard protocol, which anybody can do. During my days, not that long ago, it was only that one person in the lab could passage the cells because there were so many variables. I mean now, I don't even have to sit with the Ph.D. students to show them how to culture ES cells. You coat the wells, acquire the media, and then the cells grow. It's as simple as that."

What have been the biggest challenges for you?

"I think this probably applies to many people in the iPS field; how can we reproduce each other's results, because reprogramming is so dependent on which model you use, which cells you start with, how you overexpress the transcription factors. There are so many little details that people ignore, and then you see different results. Moreover, we are working on the human model. Others work on the mouse model, so they do not always translate. Whether this is due to species differences or because reprogramming human cells is mainly limited to the primary model (infect cells with viruses) and therefore more heterogeneous. I think we are still struggling with explaining the mechanism of reprogramming mainly due to these species and reprogramming model differences. We do a lot of genomics to get to the core of this but the problem with generating large data is the validations. I think that's probably our greatest challenge."

Looking back in your career so far, what is the biggest thing for you or what are you most proud of? Is there anything that pops out?

"I think I'm probably most proud of my first discoveries of how the Yamanaka factors interact with the genome, and the same methodology has now been applied to study so many other factors in different reprogramming models. We never predicted this, it wasn't even planned as the main project, and it ended up being the main thing. To publish a big paper that's well respected in the field, it opens doors for you. There's no doubt that publishing new and exciting discoveries is what science is all about. I think, yeah, I'm so proud of that paper. It was published in 2012 and it remains to be highly cited in our field, which I hope reflects the fact that people still find it useful and relevant. Whatever we found at that time still applies."

What is in the pipeline for you for the next 2 or 5 years? What do you hope to see?

"We are interested in designing reprogramming factors, trying to define what makes a reprogramming factor, and how to understand enough about it to go and design it from scratch."

What kind of activity is it that you feel most happy doing?

"I would love to go back to the lab and do experiments. I would love to be able to have that kind of privilege to follow a question through and find the answer, knowing that nobody else knows that answer; to see that something

HIGHLIGHTED PUBLICATION

Facilitators and impediments of the pluripotency reprogramming factors' initial engagement with the genome. Soufi A. et al.
Cell, 2012, doi: 10.1016/j.cell.2012.09.045

In this article, the authors report a map of the transcription factors (TF) Oct4, Sox2, Klf4, and c-Myc, on the human genome during the first 48 hours of reprogramming fibroblasts to pluripotency. The results reveal that the progression to pluripotency requires reorganization of the initial network for c-Myc, a shift to promoter binding by all four transcription factors, and to overcome broad heterochromatic features that occur in the somatic cell genome.

you discovered, other people find it useful and exciting. Doing bench work free you from grant writing, and getting the funding, and worrying about whether your manuscript will be accepted for publication in a top journal."

If you had an unlimited amount of funding, what would you do?

"I would hate that! It comes with too much responsibility. The question should be; what are the big ideas that a lot of money should be invested in? I think that our limited creativity and imagination will be more exposed if we have unlimited funding, we might just end up doing a lot of silly stuff. Nevertheless, if I had unlimited funding, I will be solely driven by curiosity and get as many scientists as possible involved so we don't run out of ideas. I will explore what else can our genome code for, beyond us humans or other animals.. My work has always been basic research-oriented rather than disease-oriented, but if I had unlimited funding I would also try and find novel ways to apply our findings and actually help somebody." •

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ABDENOUR SOUFI ON THE FUTURE

? It's 20 years since the first ES cells line was derived, and the innovation of the iPS cells was in 2006. If we put these cells into context of use for regenerative medicine, do you think it will be as big as we hope it will be?

! "We definitely see the potential, it's so close, and yet it's so far away. There are so many things that we need to sort out first. We need to make functional cells from these so-called pluripotent stem cells, whether ES lines or iPS lines. These stem cells are clearly not 100% pluripotent, because some of them only differentiate to neurons and others can only make blood and so on. We still don't know why this is, you might think it's epigenetic memory, although there is evidence for and against that. So, even though we call them pluripotent, they are not as pluripotent as we think they are. I think solving such problems is the next step, but this does not take anything away from the derivation of ES and iPS cells. These discoveries have made a permanent and positive impact on the field of regenerative medicine. To me, ES and iPS cells made regenerative medicine a reality."


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